VERIFICATION OF TRANSLATION

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declare as follows:

1. That I am well acquainted with both the English and German languages, and

2. That the attached document is a true and correct translation to the best of my knowledge and belief of:

   Priority document of the German patent application 102 15 131.8

Munich, 24 January 2007
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(Date)

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(Dirk Bühler)

(No witness required)

MATRIX FOR UNIFORM AND INDEPENDENT SUSTAINED RELEASE OF ACTIVE INGREDIENTS

The invention relates to a pharmaceutical formulation that is stable in storage and comprises at least one active pharmaceutical ingredient in an essentially non-swelling diffusion matrix, whereby the active ingredient(s) is/are released from the matrix with a prolonged effect, uniformly and independently in the presence of multiple active ingredients. With regard to its essential release properties, the matrix is characterized by the fact it contains ethyl cellulose and at least one fatty alcohol.

Furthermore, the invention relates to processes for producing pharmaceutical formulations that are stable in storage and contain at least one active pharmaceutical ingredient in a non-swelling diffusion matrix, whereby the active ingredient(s) is/are released from the matrix with a prolonged effect, uniformly and independently in the presence of multiple active ingredients.

Sustained-release formulations of pharmaceutical drugs play a central role in the development of improved therapeutic forms. The goal of all sustained-release dosage forms is to achieve a longer duration of the pharmacological response after administration of a medication than can be achieved by administering a medication formulated for immediate release of the active ingredient. Sustained-release dosage forms containing a relatively high dose of active ingredient which they release in a controlled manner over a long period of time (typically 2 to 16 hours) ensure that the number of times the medication must be taken by the patient is reduced and therefore patient compliance is increased.

The longer release period and thus the longer lasting effect of the active ingredients, which is ensured by the sustained-release dosage forms, is also responsible for many therapeutic advantages that cannot be achieved by short-acting, rapid release dosage forms. For example, the treatment can be continued overnight by using sustained-release dosage forms without having to interrupt the patient's sleep. This plays a role in the treatment of epilepsy patients, for example, in whom this makes it possible to prevent the occurrence of nocturnal seizures. Likewise patients who suffer from chronic pain are allowed undisturbed rest at night in this way.

From a medical and pharmacological standpoint, one advantage of sustained-release forms is to be found in the very uniform blood levels of the active ingredient which lead to a long-lasting effect and reduced adverse effects. The reduction in adverse effects plays an important role when using opioids in pain therapy, for example. The adverse effects occurring with the use of opioids include, among other things, the risk of developing an addition. Since the dependency potential of an active ingredient is defined not only by the active ingredient per se but in particular by the dosage form and the pharmacodynamics associated with that dosage form (e.g., due to the speed of flooding of the brain with the active ingredient), the dependency-inducing potential of such active ingredients can be reduced by the prolonged release of an opioid analgesic (Nolte, T.: STK-Zeitschrift für angewandte Schmerztherapie [STK Journal for Applied Pain Therapy], 2001, Vol. 2).

Due to the fact that sustained-release forms allow uniformly high blood levels of the active ingredient, the bioavailability of the active ingredient is increased. A number of factors contribute toward the bioavailability of an active ingredient. These include the active ingredient concentration in the respective physiological fluid (e.g., in the blood), the absorbability of the active ingredient through membranes (e.g., in absorption in the gastrointestinal area) and the availability of the active ingredient in the desired tissue area.

In order for an active ingredient to be absorbable in the intestinal area, for example, it must be in solution. The period of time required by a certain component of an active ingredient which is present in the unit dose of a dosage form to be dissolved in the corresponding physiological fluid is referred to as the dissolving time or as the release time, i.e., the release rate. The dissolving time of an active ingredient is determined as the percentage amount of the active ingredient released by the dose unit over a certain period of time. This determination is performed by using established measurement methods under standardized conditions. The physiological fluid in which the dissolving time of the active ingredient is determined may be, for example, the fluid of the gastrointestinal system. Many satisfactory test methods are known from the state of the art for determining the dissolving time of pharmaceutical compositions (and accordingly the rates of release of the active ingredients). These test methods are described in official compendia through the world.

The various factors that influence the dissolving time of pharmaceutical compositions and thus influence the release rate of active ingredients include, among others, the surface area of the pharmaceutical composition that is accessible to the solution medium, the pH of the solution medium, the solubility of the active ingredient in the solution media and the saturation concentrations of dissolved materials in the solution medium.

Despite the varied factors which influence the dissolving of an active ingredient in the solution medium as well as the absorption of the active ingredient, it has been shown that there is a good correlation between the *in-vitro* dissolving time of a dosage form and the *in-vivo* bioavailability of an active ingredient. This correlation is so well established that the dissolving time (rate of release of the active ingredient) is considered a generally accepted criterion for the bioavailability of an active ingredient of a pharmaceutical drug formulation. In view of this terminology, it is clear that the release rate, as determined for the active ingredient of a pharmaceutical formulation, is one of the important fundamental properties that must be taken into account when evaluating sustained-release formulations.

In the state of the art, various measures are known which allow the formulation of sustained-release dosage forms. These measures have in common the fact that the active ingredients are processed with excipients to form molded articles, e.g., tablets or pills. The excipients form a release barrier and/or dissolution barrier for the active ingredient. Depending on the type of release barriers, various sustained-release methods can be differentiated. For example there are osmotic systems, systems in which the sustained-release effect is achieved by coating or systems in which the active ingredients are embedded in waxes, polymethacrylates, gel-forming agents or silicas. In addition, there is the so-called matrix form which is especially important in formulating sustained-release dosage forms. The matrix form is a structure in which in active ingredient is bound to inert excipients if possible. Depending on the type of matrix, a distinction can be made between swelling matrices and non-swelling matrices, for example. The matrices also differ for example, in whether the active ingredient is released by pure diffusion or by erosion of the matrix (U. Schöffling, The Theory of Dosage Forms, 1998, 3rd edition, Deutscher Apotheker-Verlag, Stuttgart).

The excipients that are used for production of sustained-release dosage forms often lead to problems, however, with regard to the stability of the dosage form over long storage

periods. For waxes, for example, it has been demonstrated that they are subject to changes so that complex precautionary measures must be taken at the time of production to prevent changes during the storage period. Dosage forms in which film coatings of polymer layers produced from aqueous dispersions are used to achieve the sustained-release effect also frequently have problems with stability in storage.

Sustained-release forms with a so-called controlled release of active ingredient are known in the state of the art, i.e., not only is the release of the active ingredients prolonged but also a predetermined release rate can be adjusted. Depending on which polymers (hydroxyalkyl celluloses, polymethacrylates or alkyl celluloses, for example) are used in the production of matrix-based sustained-release dosage forms with controlled release, for example the release properties of the particular active ingredients may differ, whereby the release behavior of the active ingredients is often difficult to predict.

In general, it should be ensured that dosage forms of a given pharmaceutical formulation will always release the particular active ingredient with the same release rates and/or release profiles in a reproducible manner even if the formulation contains different absolute amounts of the active ingredient. However, this is often not the case because of the stability problems which are due to the substances used to achieve the prolonged release.

There are a variety of sustained-release formulations for a wide variety of therapeutic applications, often containing only one active ingredient. For example, the medication Oxygesic® which is used for pain therapy contains oxycodone as the only active analgesic component. The medication Kapanol® which is also used for pain therapy contains morphine sulfate as the active analgesic component.

A conventional strategy in treatment of a wide variety of symptoms is to counteract the adverse effects often induced by an active ingredient by concomitant administration of another active ingredient that specifically diminishes these adverse effects. For example, when using opioid analgesics in pain therapy, in addition to the above-mentioned risk of developing an addiction or dependency, there are often adverse effects such as constipation and respiratory depression. Therefore, there have been attempts to counteract the addictive and habituation potential and/or to eliminate or at least

significantly reduce the other adverse effects of opioid analgesics by concomitant administration of an antagonist that counteracts the opioid analgesic.

Because of the great advantages of such combination preparations and the general advantages of sustained-release dosage forms mentioned above, there is a great demand for sustained-release formulations of such combination preparations. Sustained-release formulations of combination preparations should ideally combine the positive synergistic effects of the different active ingredients with the long-lasting release and increased duration of effect accordingly.

One example of a combination preparation from which several active ingredients are released with a sustained effect is the preparation Valoron® from the company Goedeke, which contains tilidine as the active analgesic component and naloxone as the antagonist.

With combination preparations there is often the problem that active ingredients with different chemical structures and physical properties are combined one matrix. This combination usually yields different release profiles for the two active ingredients. The release of the two active ingredients with the same release profiles may be desirable from a medical standpoint, however. At the same time, however, the two active ingredients must be released from the same matrix because in this way it is possible to produce divisible tablets, for example, that are suitable for an individual dose and the manufacturing process of the corresponding dosage form is greatly simplified. In addition, when there are multiple active ingredients having different structures, the active ingredients may differ with regard to their stability in the matrix with prolonged storage times. Furthermore, with such combination preparations, a change in the amount of one component may alter the release profile of the other components in an unpredictable manner, which means a considerable increased complexity in the production of medications having different strengths of the active ingredient because it is impossible to deduce the release behavior of one preparation from the release behavior of the other preparation.

Pharmaceutical drugs must be formulated in general so that the active ingredients and the other components of the formulation are stable for the longest possible time under standard storage conditions and the intended release profiles of the active ingredients do not change even after prolonged storage time.

In addition, it should be ensured that the release profile of an active ingredient in a given sustained-release formulation will not change as a function of the quantity of active ingredient. This is true of the case when a single active ingredient is used or when multiple active ingredients are present in the dosage form.

In addition, it should be possible to select the release profile of the individual active ingredient (even in active ingredient combinations). The measures to be taken to do so should not make it difficult or even prevent the release profile of other active ingredients from being selectable as needed. Thus there should not be any mutual dependence of the release rates.

For many different therapeutic applications, there is a great demand for combination preparations. In particular for pain therapy, combination preparations consisting of opioid analgesics and corresponding antagonists are needed, whereby the corresponding dosage forms should release both active ingredients in a prolonged manner and should have the aforementioned properties. Matrix formulations that ensure a prolonged release of active ingredients in general and opioid analgesics and their antagonists specifically and have the properties mentioned above are not known in the state of the art.

German Patent Application DE 4 325 465 A1 relates to the treatment of adverse effects during pain therapy by a preparation consisting of an opioid agonist and an antagonist. The characterizing feature of this known teaching is that the antagonist must not be released with a prolonged, whereas the opioid agonist should be released with a prolonged effect.

International Patent Application WO 99/32120 also relates to a preparation consisting of an opioid analgesic and an antagonist. According to this disclosure, both active ingredients should be released with a prolonged effect. The stability in storage and the mutual dependency of the release profiles of active ingredients are not discussed in that patent application.

The above-mentioned analgesic Valoron® is a tilidine/naloxone combination. According to information provided by the manufacturing company, this is a formulation from which both active ingredient components are released with a prolonged effect. The matrix used for this purpose has a relevant content of water-swellable material

(hydroxypropyl methyl cellulose (HPMC)) and therefore is considered to be a swellable (and possibly eroding) diffusion matrix. One disadvantage of this known formulation is that tilidine and naloxone have different release profiles in the same ratios but different absolute quantities when the release is measured at a certain pH. The release rates of agonist and antagonist are not independent of one another, which is seemingly due to the sustained-release formulation that is used. It is thus necessary for a treating physician, for example to perform complex titration experiments for each individual patient when it is necessary, for example, to increase the dose despite the same tilidine/naloxone ratio because it cannot be assumed that the release behavior of the two active ingredients will remain constant. The spectrum of therapeutic quantities of the analgesic available for the treating physician is limited.

The object of the present invention is to make available formulations for pharmaceutical preparations that will ensure the sustained release of active ingredients of the preparations from the preparation while remaining stable over a long storage time and without any change in the release of the active ingredient even when different amounts of the active ingredient are used. In addition, one object of the present invention is to make available formulations for pharmaceutical preparations having the aforementioned properties and to ensure that when there are all multiple active ingredients, there is no mutual dependency of the release properties of the active ingredients.

Another object of the present invention is to make available methods for manufacturing pharmaceutical formulations containing at least one active pharmaceutical ingredient from which the active ingredients are released with a prolonged effect, in a reproducibly uniform manner and, in the case where there are multiple active ingredients, independently of one another, whereby the formulations also remain stable even with a prolonged storage time.

One object of the present invention is in particular to make available formulations for pharmaceutical preparations which contain the opioid antagonist naloxone, whereby the active ingredient is stable over a long storage time and is released from the preparation with a prolonged effect and uniformly in a reproducible manner. No formulations that accomplish this are known in the state of the art.

An additional object of the present invention is to make available formulations for pharmaceutical preparations for pain therapy containing at least one opioid analgesic

and at least one antagonist that counteracts the opioid analgesic, whereby the formulation is stable over a long period of storage and the active ingredients are released from the preparation with a prolonged and uniform effect that is reproducible and independently of one another.

The features of the independent patent claims serve to achieve this object as well as other objects derived from the description of the present invention. Advantageous embodiments of the present invention are defined in the subclaims.

The objects are achieved according to this invention by making available a pharmaceutical formulation that comprises at least one pharmaceutically active compound in an essentially non-swellable matrix and wherein the essential release properties of the matrix are characterized by ethyl cellulose and at least one fatty alcohol. It has namely been surprisingly found that only formulations with a (basically) non-swellable diffusion matrix based on ethyl cellulose and at least one fatty alcohol ensure a sustained, invariant release of active ingredients which is independent of the presence of multiple active ingredients.

The inventive matrix formulation which is stable over long periods of storage ensures in a permanent manner that the active ingredients are always released in predeterminable percentage amounts without any mutual influence of these rates of release. In combination preparations containing, for example, opioid analgesics and corresponding antagonists, this prevents abuse of the medication for one thing because abuse presupposes that the agonist can be selectively extracted from the formulation. With the formulation according to this invention, it is hardly possible regardless of the absolute and relative amounts of the active ingredients selected, to leach one active ingredient out of the preparation without the corresponding other active ingredient. In addition, such preparations reduce the adverse effects which normally occur with the use of opioids. Since the active ingredients are released from the same matrix, a simplified and efficient production process is possible. This is of course also true of the combination preparations which contain other active ingredients than opioid analgesics or their antagonists.

In addition, the inventive formulation of a pharmaceutical drug ensures in particular that the active ingredients with the same quantity ratios will exhibit the same release behavior independently of the absolute quantity present. Such release behavior allows

the physician a broad spectrum of absolute quantities of active ingredients that may be used with known optimum active ingredient ratios (e.g., opioid agonist/antagonist ratios). This provides the possibility of convenient individualized adjustment of dose to the given patient for an incremental increase in dose as well as, if necessary, incremental reduction in dose. This individualized dosage for the given patient, like the increased compliance, is extremely appropriate from a medical standpoint.

Inventive formulations also allow the production of dosage forms which release active ingredients of different structures having the same release profiles.

Since the predefinable release of the active ingredients from the inventive formulation does not change regardless of the quantity or number of active ingredients and since the active ingredients are released from the same matrix, preparations with different quantities of active ingredient can be produced without any great technical complexity once the active ingredient combinations have been established, and corresponding preparations can be made available for different therapeutically relevant ranges.

The essential features of the present invention include the sustained, invariant and independent release of active ingredient components (in the case when multiple active ingredients are present simultaneously) from a diffusion matrix that is a non-swellable matrix, at least it is not swelling to an extent that will be relevant for the release, whereby the essential release properties of the matrix are determined by ethyl cellulose and at least one fatty alcohol, and the active ingredients remain stable over long periods of storage.

The terms "prolonged-release" and/or "sustained-release" as used according to this invention are understood to refer to the release of active ingredient components of a pharmaceutical drug over a longer period of time than would occur from dosage forms formulated for immediate release of the active ingredients. Release over a period of two to twenty hours is preferred here, especially preferably over two to sixteen hours or two to twelve hours, whereby the specifications must comply with statutory regulations.

The term "prolonged release" does not refer to controlled release at a defined location, i.e., the active ingredients being released in a targeted manner either only in the stomach or only in the intestinal area. Accordingly, the release of active ingredients from the inventive formulations proceeds independently of pH. (Such local release may of course

be additionally achieved in the individual case, e.g., by enteric coating of the pharmaceutical drug. As a rule, however, according to the information available today, this is not usually advantageous.)

The term "independent release" is understood according to this invention to mean that in the presence of at least two active ingredient components, the change in the absolute amount of a component does not have any influence on the release profiles of the other components and these remain essentially unchanged. Such an independent release behavior with the inventive formulations is independent of the pH at which the release is measured or the type of manufacturing process used for the formulation. In particular, the pH independence exists in the acid range, i.e., at a pH of <7. The release profile (and/or behavior) is understood to refer to the release of the active ingredient from the formulation over a period of time, expressed in percentage of the absolute content of this active ingredient, as determined with conventional tests.

In concrete terms this means, for example, that the release profile of oxycodone observed with an oxycodone/naloxone combination of 12 milligrams of oxycodone and 4 milligrams of naloxone does not change when a corresponding preparation contains 12 milligrams of oxycodone but 6 milligrams of naloxone with the same formulation.

The terms "invariant release behavior" and/or "release profile" are understood according to this invention to mean that the percentage amount of the absolute content released from the active ingredient per unit of time does not change significantly and remains sufficiently constant even if the absolute contents changed. The phrase "sufficiently constant percentage amounts" is understood to mean that the percentage amount of substance released per unit of time does not vary from the average by more than 20%, preferably by no more than 15% and especially preferably by no more than 10%. The average is determined by measuring six release profiles. The quantity of substance released per unit of time must of course meet the specifications established by law.

In concrete terms, this means that with an oxycodone/naloxone combination of 12 mg oxycodone and 4 mg naloxone, for example, 25% oxycodone and 20% naloxone are released within the first four hours, and even with an oxycodone/naloxone combination of 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 20% naloxone are released within the first four hours, and the deviation in both cases is no greater than 20%, based on the mean value (in this case 25% for oxycodone and 20% for naloxone).

The term "storage stable" as used in the present invention is to be understood to mean that after storage under standard conditions (at least two years at room temperature and the usual humidity), the active ingredient contents of a pharmaceutical drug formulation do not differ from the initial contents by more than the values stipulated in the specifications and/or pharmacopoeia specifications. The term "storage stable" is also to be understood according to this present invention to mean that a preparation produced according to the present invention can be stored under standard conditions (60% relative humidity, 25°C) in a manner that conforms to approval specifications.

The term "storage stable" according to the present invention is also to be understood to mean that active ingredient components have a release profile after a storage time under standard conditions just like they would have if used directly without storage. The fluctuations with regard to the release profile are characterized according to this invention by the fact that the quantity of substance released per unit of time must not vary from an average value by more than 20%, preferably by no more than 15% and especially preferably by no more than 10%. The average is determined by measuring six release profiles.

The term "storage stability" thus refers to the active ingredients as well as the other components of an inventive formulation and therefore to the formulation as a whole.

The release of active ingredients from a sustained-release formulation is preferably measured by means of HPLC by using the basket method according to USP at pH 1.2 or pH 6.5.

To determine the stability in storage, the corresponding release rates are measured by means of HPLC using the basket method according to the USP at pH 1.2.

The term "formulation" as used according to this invention is understood to refer to the preparation of an active pharmaceutical substance with excipients (formulation excipients) with the goal of allowing an application, distribution and manifestation of the effects of the active ingredient that are coordinated optionally with the particular application.

A "non-swellable" and/or "essentially non-swellable" diffusion matrix is understood according to the present invention to refer to a matrix formulation in which the release of active ingredients is not influenced at all or at least is not influenced to any relevant extent by swelling of the matrix (in particular in the physiological fluid at the determination site in the patient's body).

It has surprisingly been found that pharmaceutical drug formulations having an essentially non-swelling diffusion matrix are capable of releasing one or more active ingredients with a prolonged, uniform effect independently of one another in the case where there are multiple active ingredients, when the diffusion matrix contains ethyl cellulose as the matrix-forming substance and in its essential release properties is formed by ethyl cellulose and at least one fatty alcohol. Such formulations are characterized by a good stability in storage. According to the information currently available, formulations with a diffusion matrix are mainly capable of releasing active ingredients in the inventive manner described above. Formulations having a (relevant) swelling diffusion matrix or an eroding matrix are not capable of doing so according to the information currently available.

Therefore, water-swellable substances and in particular water-soluble polymers are not usually used as matrix-forming substances to produce matrices for the inventive formulations. In particular, conventional matrix-forming polymers are used, e.g., polyvinylpyrridone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, poly(vinyl alcohol), alginates, hydrogenated hydroxyalkyl cellulose and hydroxypropylmethyl cellulose ethers according to the information currently available these substances are not suitable for production of inventive formulations.

Matrix-forming substances capable of forming non-swelling diffusion matrices can be used for producing inventive formulations if they ensure the inventive release profile of the active ingredients, i.e., prolonged and uniform release and, if there are multiple active ingredients, independent release as well as stability of the formulation in storage. Water-insoluble polymers which are usually used to produce sustained dosage forms having a matrix also cannot readily be used for production of the inventive formulation. According to the information currently available, the usual matrix-forming substances cannot be used for production of the inventive formulations, including acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl

methacrylate copolymers, cyanoethyl meth-acrylates, aminoalkyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid), polymethacrylates, poly(methyl methacrylate) copolymers, polyacrylamines or alginic acids.

Matrices based on polymethacrylate (e.g., Eudragit® RS30D and Eudragit® RL30D) or those containing relevant amounts of water-swellable material, in particular hydroxyalkyl celluloses such as HPMC, will not be used according to this invention based on the information currently available.

Likewise, according to the information currently available, alkyl celluloses are not generally used for the inventive formulations. Propyl cellulose, for example, is too lipophilic to obtain matrices with inventive release properties. Methyl cellulose is also less suitable for the inventive formulations.

According to this invention, the matrix which ensures sustained release of the active ingredients is to be selected so that the release of the active ingredients takes place with a prolonged effect, invariant and, if multiple active ingredients are present, independent of one another, and the formulation must be stable in storage. Preferably such inventive matrices include polymers based on ethyl cellulose. Ethyl cellulose itself is especially preferred. In particular, matrices using such polymers as those commercially available under the brand name Surelease® E-7-7050 are especially preferred.

Other sustained-release principles, e.g., sustained-release film coatings are also not suitable according to the information currently available for producing formulations that have an inventive release profile of active ingredients and ensure that the formulation is stable in storage.

With the inventive formulations having a non-swelling diffusion matrix based on ethyl cellulose, the ethyl cellulose content (and/or Surelease® E-7-7050) in the matrix should be between 1% and 15%, preferably between 3% and 12%, in particular preferably between 5% and 9%, most preferably between 6% and 8%. The percentage amounts are based on percent by weight.

Inventive formulations contain in addition to ethyl cellulose as the second sustained-release component at least one fatty alcohol. This may be, for example, lauryl alcohol, myristyl alcohol, stearyl alcohol, cetylstearyl alcohol, ceryl alcohol and/or cetyl alcohol.

The preferred fatty alcohols are stearyl alcohol and/or cetyl alcohol. The fatty alcohol content in the matrix is between 5 and 30%, preferably between 10% and 25% and especially preferably between 15% and 20%. A fatty alcohol content of essentially 20% in production of the matrix by spray granulation and essentially 18% in production of the matrix by extrusion is especially preferred. The percentage amounts given are percent by weight.

Inventive formulations may also contain other sustained-release components as needed, as long as it is ensured that they will not have a negative effect on the inventive release of the active ingredients from the formulation or the stability of the formulation in storage. Such additional sustained-release components include preferably polyalkylene glycols, especially preferably polyethylene glycols.

In addition to the matrix-forming polymer and the fatty alcohol, the inventive formulations may also contain fillers and excipients such as granulation aids, lubricants, coloring agents and flow agents as well as plasticizers, if they do not have a negative effect on the release properties and storage stability of the inventive formulation.

Suitable fillers include sugars such as lactose, glucose or sucrose, starches and their hydrolysates, microcrystalline cellulose, cellactose, sugar alcohols such as sorbitol or mannitol, sparingly soluble calcium salts such as calcium hydrogen phosphate, dicalcium phosphate or tricalcium phosphate.

Povidone, for example, may be used as the granulation aid.

Preferably highly dispersed silica (Aerosil®), talc, cornstarch, magnesium oxide, magnesium stearate or calcium stearate is used as the flow agents or lubricant. Suitable lubricants preferably include magnesium stearate and/or calcium stearate. Fatty acids, e.g., stearic acid, or fats, e.g., hydrogenated castor oil, may also be preferred. In addition, polyethylene glycols may be considered as preferred lubricants.

Other suitable pharmaceutical excipients that are conventionally used according to the state of the art, such as wetting agents, preservatives, diluents, granulation aids, coloring agents, flavorings, detergents, buffers and/or antistick agents may also be present in the controlled-release matrix inasmuch as the formulation manifests an inventive release profile, i.e., the prolonged, uniform release of the active ingredients, independent

release if there are multiple active ingredients and they are stable in the matrix during storage.

When using the aforementioned fillers and excipients such as coloring agents and the aforementioned lubricants and internal lubricants, flow agents and plasticizers, it is important to be sure that only those combinations that ensure the inventive release properties and the stability of the formulation in storage may be used according to this invention together with the matrix-forming substance and the fatty alcohol.

All these formulation ingredients will be selected in such a way that the release matrix assumes the character of a diffusion matrix that is essentially non-swelling in water and is also known eroding.

According to this invention, a suitable formulation containing ethyl cellulose or Surelease® E-7-7050 and stearyl alcohol as the matrix-forming component, magnesium stearate as the flow agent, lactose as the filler and povidone as the granulation agent is especially preferred.

It is thus possible to produce preparations which release the active ingredients with a sustained effect, independently, uniformly and in equal amounts per unit of time can thus also be produced with the matrices according to this invention. In concrete terms, this means that with an oxycodone/naloxone combination of 12 mg oxycodone and 4 mg naloxone, for example, 25% oxycodone and 25% naloxone will be released within the first 4 hours, and with an oxycodone/naloxone combination of 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 25% naloxone will be released within the first 4 hours, whereby in both cases the deviation is no greater than 20%, based on the mean value (in this case 25% oxycodone and/or naloxone).

Such identical release behavior of the two active ingredients may be desirable under certain medical conditions.

The inventive formulation may be used to produce preparations in any conventional dosage form that is fundamentally suitable for sustained formulations and ensures release of the active ingredients in the manner according to this invention. Tablets, including multilayer tablets and capsules are especially suitable. However, dosage forms

such as granules or powders may also be used, but only those dosage forms having an adequate delayed release and inventive release behavior are allowed.

As needed, the dosage form formulated according to this invention may have film coatings, in which case it must be ensured that the film coatings do not have a negative effect on the release properties of the active ingredients from the matrix or the stability of the active ingredients in the matrix during storage. Such film coatings may be colored, for example. Such film coatings may also contain an initial dose of the active ingredients, as needed. The active ingredients contained in the initial dose are released immediately after taking the medication and therefore the therapeutically effective blood plasma levels are reached very rapidly. It is important here to ensure that further release of the active ingredients from the matrix is not influenced in a negative sense by the coating of the dosage forms formulated according to the present invention.

The active ingredients which are contained in an inventive formulation and are released from the inventive matrix in a sustained and invariant manner, and when several agents are present simultaneously, in an independent manner and are stable in this matrix during storage are not limited to a special class of agents. For example, they may be antipyretic, analgesic and/or anti-inflammatory agents, ulcer-inhibiting agents, coronary vasodilating agents, peripheral vasodilating agents, antibiotics, synthetic antimicrobial agents, antispasmodic agents, antitussive and/or antiasthmatic agents, bronchodilating agents, diuretic agents, muscle relaxants, so-called minor tranquilizers, so-called major tranquilizers, beta-blockers, antiarrhythmics, taste-inhibiting ingredients, anticoagulants, anti-epileptics, antihistamines, antiemetics, antihypertensives, sympathomimetics, expectorants, oral antidiabetics, systemic cardiovascular agents, vitamins, agents for pollakiuria and/or inhibitors for angiotensin-converting enzymes.

Inventive formulations containing opioid analgesics (opioid agonists) and/or opioid antagonists as the active ingredients are especially preferred.

According to this invention, opioid analgesics or opioid agonists are understood to include all substances belonging to class NO2A of opioid analgesics according to the ATC classification of the WHO and which manifest an analgesic action when administered appropriately. An opioid agonist is preferably from the group comprising morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives

thereof, methadone, dextropropoxyphen, buprenorphine, pentazocine, tilidine, tramadol, hydrocodone. Additional examples of analgesics include meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, metopone, levorphanol, phenazocine, etoheptazine, propiram, profadol, phenampromide, thiambutene, pholcodeine, codeine, dihydrocodeinone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy-Δ'-cyclohexene, 3-dimethylamino-0-(4-methoxyphenylcarbamoyl)propiophenone oxime, (-)β-2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzo-morphan, (-)2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)α-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindole 2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3(m-hydroxy-phenyl)-piperidine, N-allyl-7α-(1-R-hydroxy-1-methylbutyl)-6,14-endoethanotetrahydronororipavine, (-)2'-hydroxy-2-methyl-6,7-benzomorphan, noracylmethadole, phenoperidine, α-dl-methadole, α-1-methadole, β-dl-acetyl-methadole, α-1-acetymethadole and β-1-acetylmethadole. This list is not exclusive.

The analgesically active opioid agonist in the inventive formulations include especially preferably oxycodone, hydrocodone, hydromorphone, morphine, codeine, dihydrocodeine, methadone, oxymorphone, fentanyl and sufentanyl. The opioid agonist is oxycodone in particular.

According to this invention, antagonists are substances that counteract the opioid agonists (as explained above). Such substances can also be found in the ATC classification of the WHO. According to this invention, The preferred substances are those which reduce the adverse effects and the habituation effects as well as the addictive potential associated with the opioid agonist when administered appropriately. These may include, for example, naltrexone, naloxone, nalmefen, nalorphine, nalbuphine, naloxonazine, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-β-naloxol, 6-β-naltrexol.

Especially preferred antagonists for the inventive formulations include naltrexone, nalmefene and naloxone. Naloxone is an especially preferred antagonist.

Formulations containing a combination of oxycodone as the agonist and naloxone as the antagonist are especially preferred according to this invention. In these formulations, the agonist is present in excess based on the unit dose amount of the antagonist in the combination preparation. The excess of the opioid agonist is usually given by stating the

weight ratio of agonist to antagonist. In the case of oxycodone and naloxone, preferred weight ratios of agonist to antagonist are in the weight ratio range from max. 25:1, especially preferably in the weight ratio ranges of 20:1, 15:1, 10:1, 5:1, 4:1, 3:1, 2:1 and 1:1.

If inventive formulations contain oxycodone and/or naloxone as active ingredients, then between 10 and 150 mg oxycodone, especially preferably between 10 and 80 mg oxycodone is used per unit dose and preferably between 1 and 50 mg naloxone is used per unit dose.

Although not always stated explicitly, the term "active compound" is always understood to include pharmaceutically acceptable derivatives, salts and the like having the same effect. For example, when referring to oxycodone or naloxone, this is understood to also include not only the base, but also its hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate, succinate and the like.

The preparations synthesized according to this invention may be administered orally, nasally and/or rectally, depending on the indication.

Inventive formations can be produced by embedding the active ingredient in the matrix, e.g., by melting, spray solidification, spray drying, granulation, direct tableting and/or extrusion.

Pharmaceutical preparations or precursors formulated according to this invention may preferably be produced by buildup and/or breakdown granulation. Spray granulation with subsequent drying of the granules is preferred. Buildup granulation in a drum or in a granulator is also preferred. The granules may then be pressed using suitable excipients to form tablets, for example. Those skilled in the art will be familiar with granulation techniques for production of dosage forms having prolonged release.

The pharmaceutical formulations or precursors thereof according to the present invention can be produced by extrusion to particular advantage (instead of by granulation) because this makes it possible to eliminate process steps (such as drying the granules in spray granulation) and the inventive formulations can be produced efficiently and inexpensively accordingly.

Since production of inventive formulations by extrusions is a continuous production process, several process steps may be omitted in comparison with other manufacturing methods, e.g., spray granulation, which makes the production of the inventive formulations more efficient.

In the production of inventive formulations by extrusion, e.g., with the omission of Surelease® E-7-7050, which contain dibutyl sebacate as a plasticizer plus additional components, ethyl cellulose may be used directly making the production process more favorable and more efficient.

To produce inventive formulations, extrusion methods using single-screw or multi-screw extruders may be used. These extruders may be co-rotating or contra-rotating screw extruders. The feed rate of the components used will depend on the particular machine. During extrusion, the temperature of the heating zones where the components of the inventive formulation are melted is 40°C to 120°C, 50°C to 100°C, preferably 50°C to 90°C, especially preferably 50°C to 70°C and most preferably 50°C to 65°C. It will be clear to those skilled in the art that it is not necessary to heat in each of the heating zones. In particular in the first heating zones downstream from the filling connection, where the components are mixed, cooling by preferably 25°C may also be necessary. The rotational speed of the screw will vary between 100 and 500 rpm, preferably between 100 and 250 rpm, especially preferably between 100 and 200 rpm and especially 150 rpm. The geometry and diameter of the nozzle opening with the extruders used may be selected as needed. The diameter of the nozzle opening of the extruders used to produce the inventive formulations will typically be between 1 mm and 10 mm, preferably between 2 mm and 8 mm, especially preferably between 3 mm and 5 mm. The types of extruders used may differ in design and may include kneading elements, for example. The ratio of the length/diameter of the screw will typically be around 40:1 with the extruders used to produce the inventive formulations. Typical screw profiles suitable for producing inventive formulations by extrusion are illustrated in Figures 1A and 1B. Those skilled in the art will be familiar with extrusion techniques for producing dosage forms with prolonged release.

In a preferred embodiment for producing inventive formulations, a contra-rotating twin screw extruder is used. This may be for example an extruder of the type Micro 18 GGL from the company Leistritz AG, Nuremberg. In this preferred embodiment, the extruder

does not have any kneading elements (see also Figure 1A). The feed rate of the substances used to produce the inventive formulation is between 1 and 3 kg/h, preferably between 1 and 2 kg/h. A feed rate of 1.5 kg/h is especially preferred. The temperature of the heating zones is preferably 40 to 120°C, 50 to 100°C, preferably 50 to 90°C, especially preferably 50 to 70°C. A temperature of 50 to 65°C is most preferred. The extruder has 10 heating zones. As a rule, the components are cooled by 25°C in the first heating zone. The temperature in the other heating zones is then preferably around 50°C to 65°C and may vary from one heating zone to the next. The screw speed varies between 100 and 500 rpm, preferably between 100 rpm and 250 rpm, especially preferably between 120 rpm and 200 rpm and especially preferably 150 rpm. The diameter of the nozzle opening varies between 1 mm and 10 mm, preferably between 2 and 8 mm or between 3 mm and 5 mm. In an especially preferred embodiment the diameter of the nozzle opening is approximately 3 mm.

In general the temperature of the heating zones is selected so that no temperatures at which the pharmaceutically active ingredients would be destroyed can occur. The feed rate and screw speed are to be selected so that the inventive formulations produced by extrusion will release the active ingredient in delayed, independent and invariant manner and the active ingredients are stable in the matrix during storage. With an elevated feed rate, under some circumstances it may be necessary to increase the screw speed accordingly to achieve a uniform sustained release effect.

For all these parameters, it is true that they depend on the particular process conditions (type of machine, screw geometry, number of components, etc.) and must be adapted so that the inventive formulations produced by extrusion will release the active ingredients in delayed, independent and invariant manner and the active ingredients are stable in the matrix during storage. Those skilled in the art familiar with extrusion techniques will be familiar with how to perform such an adjustment of the parameters.

Production of inventive formulations by extrusion is preferred, whereby the formulations contain opioid analgesics and opioid antagonists as the active ingredients. Production of invention formulations containing oxycodone and naloxone is especially preferred, whereby preferred weight ratios of agonist to antagonist are in the weight ratio range of max. 25:1, especially preferably in the weight ratio ranges of 20:1, 15:1, 10:1, 5:1, 2:1 and 1:1.

Examples representing especially preferred embodiments of the present invention are described below. In addition, examples showing that inventive formulations differ essentially in their structure from formulations with a sustained release produced using conventional matrix-forming polymers are also given below. Only the formulations produced according to the present invention have a sustained, invariant and, in the presence of multiple active ingredients, independent release of the active agents, with the formation being stable in storage. The examples are not to be interpreted restrictively in any way.

Example 1 – Production of tablets with different amounts of oxycodone/naloxone with a non-swelling diffusion matrix by spray granulation:

The following amounts of the components listed were used for inventive production of oxycodone/naloxone tablets:

Preparation (name)	Oxy/Nal-0	Oxy/Nal-5	Oxy/Nal-10
Oxycodone HCl	20.0 mg	20.0 mg	20.0 mg
Naloxone HCl	-	5.0 mg	10.0 mg
Lactose Flow Lac 100	59.25 mg	54.25 mg	49.25 mg
Povidone 30	5.0 mg	5.0 mg	5.0 mg
Surelease	10.0 mg solids	10.0 mg solids	10.0 mg solids
Stearyl alcohol	25.0 mg	25.0 mg	25.0 mg
Talc	2.5 mg	2.5 mg	2.5 mg
Mg stearate	1.25 mg	1.25 mg	1.25 mg

The Surelease® E-7-7050 polymer mixture used had the following composition:

Surelease® E-7-7050
Ethyl cellulose 20 cps
Dibutyl sebacate
Ammonium hydroxide
Oleic acid
Silicon dioxide
Water

Oxycodone HCl, naloxone HCl, povidone 30 and Lactose Flow Lac 100 were mixed in a free-fall mixer (Bohle) and then spray-granulated with Surelease® E-7-7050 in a fluidized bed granulator (GPCG3) to produce the tablets. The material was then passed through a Comill 1.4 mm screen. In addition, a granulation step was performed using molten fatty alcohol in a forced mixer (Collette Gral). All the tablet cores produced in this way have a weight of 123 mg based on the dry substance.

Example 2 – Production of tablets with oxycodone and naloxone in a non-swelling diffusion matrix by extrusion:

The following amounts of the components indicated were used for the inventive production of oxycodone/naloxone tablets by extrusion:

Preparation (name)	Oxy/Nal-Extr
Oxycodone HCl	20 mg
Naloxone HCl	10 mg
Collidone 30	6 mg
Lactose Flow Lac 100	49.25 mg
Ethyl cellulose 45 cpi	10 mg
Stearyl alcohol	24 mg
Talc	2.5 mg
Mg stearate	1.25 mg

The stated amounts of oxycodone HCl, naloxone HCl, ethyl cellulose 45 cpi, Collidone 30, Lanette 18 and Lactose Flow Lac 100 were weighed into a Bowle free-fall mixer and mixed there. Then this mixture was extruded through a contra-rotating twin-screw extruder of the type Micro 18 GGL from the company Leistritz AG, Nuremberg. The temperature of heating zone 1 was 25°C, that of heating zone 2 was 50°C, that of heating zones 3 through 5 was 60°C, that of heating zones 6 through 8 was 55°C, that of heating zone 9 was 60°C and that of heating zone 10 was 65°C. The wound gear speed was 150 rpm, the resulting melt temperature was 87°C, the feed rate was 1.5 kg/h and the diameter of the nozzle opening was 3 mm. The extruded material was passed through a Frewitt 0.68 × 1.00 mm screen. This milled extrudate was mixed with talc and magnesium stearate, passed through a 1 mm hand screen and pressed to form tablets. The extruder had a screw geometry like that illustrated in Figure 1A.

In comparison with the production of oxycodone/naloxone tablets likewise having a non-swelling diffusion matrix based on Surelease® by spray granulation (see Example 1), the extruded preparation contains fewer components in the product.

Example 3 – Release behavior of oxycodone/naloxone tablets from Example 1:

Release of the active ingredients was investigated by means of HPLC over a period of 12 hours using various tablets Ox/Nal-0, Ox/Nal-5 and/or Ox/Nal-10 according to the basket method as described in USP at pH 1.2.

Figure 2 and the values given in the table show that in the case of a non-swelling diffusion matrix based on Surelease®, the release of oxycodone remains the same regardless of the amount of naloxone. Likewise, uniform release profiles are obtained from naloxone with different amounts of oxycodone.

Time (min)	Ox/Nal-0	Ox/Nal-5-O	Ox/Nal-5-N	Ox/Nal-10-O	Ox/Nal-10-N
	Oxy	Oxy	Nal	Oxy	Nal
0	0	0	0	0	0
15	26.1	24.9	23.5	22.8	24.1
120	62.1	63	61	57.5	60.2
420	91.7	94.5	91.9	89.4	93.5
720	98.1	99.6	96.6	95.7	100.6

The release values are based on oxycodone or naloxone (line 2) and are given in percentage amounts. The mean value of the release of naloxone, for example, is 92.7% at 420 minutes. The maximum deviation at this measurement point in time is 1%. "Oxy" and "Nal" stand for oxycodone and naloxone, respectively, and indicate the particular active ingredient being investigated.

Example 4 – Release behavior of oxycodone/naloxone tablets from Example 2 at various pH levels:

The release of the active ingredients from the tablets was investigated by means of HPLC over a period of 12 hours at pH 1.2 and for a period of 1 hour at pH 1.2 and then for 11 hours at pH6.5, using the basket method according to USP.

The following release rates were obtained at 12 hours and pH 1.2:

Time (min)	Oxy/Nal-Extr-1.2-O	Ox/Nal-Extr-1.2-N
	Oxy	Nal
0	0	0
15	24.1	24.0
120	62.9	63.5
420	92.9	93.9
720	96.9	98.1

The following release rates were obtained at 1 hour and pH 1.2 and 11 hours and pH 6.5:

Time (min)	Oxy/Nal-Extr-6.5-O	Ox/Nal-Extr-6.5-N
	Oxy	Nal
0	0	0
60	48.1	49.2
120	65.0	64.7
240	83.3	81.8
420	94.1	92.3

The release values are based on oxycodone or naloxone (line 2) and are given in percentage amounts. "Oxy" and "Nal" stand for oxycodone and naloxone, respectively, and indicate the particular active ingredient being investigated.

First, it is clear from a comparison of the values given in the tables of Example 4 and the table of Example 3 that regardless of the production process, the active ingredients

are released from the preparations in uniform amounts. For example, after 420 minutes, 89.4% of oxycodone has been released from spray granulated tablets (Ox/Nal-10 tablets, see Example 3) and after 420 minutes 92.9% has been released from the extruded tablets (Oxy/Nal-Extr 1.2-O, Example 4). The deviation in the release of oxycodone from extruded tablets thus differs by 1.1% from the mean value of the release of oxycodone from spray-granulated tablets (91.9% at 420 minutes). At 420 minutes, 93.5% naloxone has been released from spray granulated tablets (Ox/Nal-10 tablets, see Example 3) and after 420 minutes 93.9% naloxone has been released from extruded tablets (Oxy/Nal-Extr 1.2-O, Example 4). The deviation in the release of naloxone from extruded tablets thus differs by 1.3% from the mean value of the release of naloxone from spray-granulated tablets (92.7% at 420 min).

In addition, a comparison of the values given in the tables of Example 4 and Figures 3A and 3B reveals that regardless of the pH at which the measurement of the release rates is performed, the release of oxycodone and naloxone likewise remains the same.

Example 5 – Comparative Example: Release behavior of Valoron® tablets:

The release of the active ingredients was investigated by means of HPLC over a period of time of 7 hours using Valoron® tablets with 50 mg tilidine and 4 mg naloxone (Ti/Nal-50/4) and/or 100 mg tilidine and 8 mg naloxone (Ti/Nal-100/8) and/or 150 mg tilidine and 12 mg naloxone (Ti/Nal-150/12) using the basket method according to USP for 1 h at pH 1.2 and then for 6 h at pH 6.5.

It can be seen from Figures 4A and 4B and the values given in the table that in the case of a swelling diffusion matrix (and possibly also eroding) with relevant amounts of HPMC, the release of various amounts of tilidine with different amount of naloxone varies significantly and is not uniform. This is also true of naloxone converse. This means that at this pH, the active ingredients are not released independently.

Time (min)	Ti/Nal-50/4-T	Ti/Nal-50/4-N	Ti/Nal-100/8-T	Ti/Nal-100/8-N	Ti/Nal-150/12-T	Ti/Nal-150/12-N
	Til	Nal	Til	Nal	Til	Nal
0	0	0	0	0	0	0
60	37.2	27.6	33.9	27.3	29.9	23.3
120	47.6	31.7	46.5	33.4	41.5	28.5
180	54.7	37.4	55	41.2	48.2	35
240	59.7	44	68.2	59.5	54.5	40.1
300	65.2	50.6	82.6	72.9	60.5	47.5
360	70.3	58	85.7	82.7	67.2	56.4
420	74.2	60.8	93.1	90.9	84.9	78.9

The release values are based on tilidine or naloxone (line 2) and are given in percentage amounts. The mean value of the release of naloxone is 78.87% after 420 minutes, for example. The maximum deviation at this measurement point in time is 20.4%. "Til" and "Nal" stand for tilidine and naloxone, respectively, and indicate the particular active ingredient investigated in each case.

Example 6 – Electron microscopic comparison of the structure of tablets from Example 1 and Example 2 with Valoron® in tablets

The tablets used for the electron microscopic analysis included tablets containing 20 mg oxycodone and 10 mg naloxone, produced either by spray granulation according to Example 1 (Ox/Nal-10) or by extrusion according to Example 2 (Oxy/Nal-Extr); a Valoron® N tablet with 100 mg tilidine and 8 mg naloxone was also tested.

Figures 5A and 5B show different enlargements of scanning electron micrographs of an Ox/Nal-10 tablet with the inventive formulation produced by spray granulation. Figures 6A and 6B show different enlargements of scanning electron micrographs of an Oxy/Nal-Extr tablet with the inventive formulation produced by extrusion. Figures 7A and 7B show scanning electron micrographs of the above mentioned Valoron® N tablet.

It can be seen clearly from a comparison of these figures that tablets with an inventive formulation have a much finer and more homogeneously structured surface with fewer cracks than the Valoron tablet regardless of whether they are produced by spray

granulation or by extrusion. This structural difference may be the reason for the difference in the release behavior of the preparations used.

Example 7 – Production of tablets with various amounts of naloxone with various matrices by spray granulation

The following amounts of the stated components were used for the production of naloxone tablets:

Preparation (name)	Nal-5-Eud	Nal-5-Sure	Nal-10-Sure
Naloxone HCl	5.0 mg	5.0 mg	10.0 mg
Lactose Flow Lac 100	74.25 mg	74.25 mg	69.25 mg
Povidone 30	5.0 mg	5.0 mg	5.0 mg
Eudragit® RS30D	10 mg solids	---	---
Surelease® E-7-7050	---	10 mg solids	10 mg solids
Triacetin	2.0 mg	---	---
Stearyl alcohol	25.0 mg	25.0 mg	25.0 mg
Talc	2.5 mg	---	---
Mg stearate	1.25 mg	1.25 mg	1.25 mg

Eudragit® RS30D is available from Röhm GmbH, Darmstadt. Surelease® E-7-7050 is available from Colorcon Ltd., Idstein.

The Eudragit® RS30D and Surelease® E-7-7050 polymer blends that were used had the following compositions:

Eudragit® RS30D	Surelease® E-7-7050
Ammoniomethacrylate copolymer B	Ethyl cellulose 20 cps
Sorbic acid	Dibutyl stebacate
Sodium hydroxide	Ammonium hydroxide
Water	Oleic acid
	Silicon dioxide
	Water

Naloxone HCl, Povidone 30 and Lactose Flow Lac 100 were blended in a free-fall mixer (Bohle) and then spray granulated with Eudragit® RS30D or Surelease® E-7-

7050 in a fluidized bed granulator (GPCG3) to produce the tablets. The material was then passed through a Comill 1.4 mm screen. In addition a granulation step using molten fatty alcohol in a forced mixer (Collette) was performed. All tablet cores produced in this way had a weight of 125 mg based on the dry substance.

Example 8 – Production of naloxone tablets with a non-swelling diffusion matrix by extrusion

The following amounts of the components listed were used for the production of naloxone tablets by extrusion:

Preparation (name)	Nal-Extr
Naloxone HCl	10.0 mg
Lactose Flow Lac 100	70.25 mg
Collidone 30	5.0 mg
Ethyl cellulose 45 cpi	8.0 mg
Stearyl alcohol	26.0 mg
Talc	2.5 mg
Mg stearate	1.25 mg

The stated amount of naloxone HCl, ethyl cellulose 45 cpi, Collidone 30, Lanette 18 and Lactose Flow Lac 100 were weighed into a Bowle free-fall mixer and blended. Then this mixture was extruded in a contra-rotating twin-screw extruder of the Micro 18 GGL type from the company Leistritz AG, Nuremberg. The temperature of heating zone 1 was 25°C, heating zone 2 was 50°C, heating zones 3 through 10 was 55°C. The screw speed was 140 rpm, the resulting melt temperature 65°C, the feed rate 1.25 kg/h and the diameter of the nozzle opening was 3 mm. The extruded material was passed through a Frewitt 0.68 × 1.00 mm screen. This ground extrudate was mixed with talc and magnesium stearate, passed through a 1 mm hand screen and pressed to form tablets. The extruder had a screw geometry like illustrated in Figure 1.

In comparison with the production of oxycodone/naloxone tablets with a non-swelling diffusion matrix based on Surelease® by spray granulation (see Example 7), the product in the extruded preparation contains fewer components.

Example 9 – Release behavior of naloxone tablets from Example 7

The release of the active ingredient was investigated by HPLC over a period of 16 hours from two tablets (labeled as A and B) each of Nal-5-Eud, Nal-5-Sure and Nal-10-Sure which had the compositions given in Example 5, using the basket method according to USP at pH 1.2.

It can be seen from Figures 8A and 8B and the values given in the table that in the case of the non-swelling diffusion matrix based on Surelease®, the release of naloxone does not change in reproducible manner regardless of the absolute amount and remains largely the same. This is also true of the release of naloxone from a matrix based on Eudragit®.

Time (min)	Nal-5-Eud-A	Nal-5-Eud-B	Nal-5-Sure-A	Nal-5-Sure-B	Nal-10-Sure-A	Nal-10-Sure-B
0	0	0	0	0	0	0
15	18.48	18.23	23.86	21.97	20.65	22.25
90	40.46	26.15	46.74	47.33	45.18	45.98
240	62.43	53.47	70.48	69.49	69.13	68.76
420	82.9	72.27	91.04	88.69	88.06	87.5
720	97.46	85.74	100.62	99.1	96.05	95.74
960	107.6	96.26	102.26	102.33	97.91	97.43

The release values are based on naloxone and are given in percentage amounts. The average value of the naloxone release is 46.3% after 90 minutes in the case of the Nal-Sure tablets. The maximum deviation at this measurement point in time is 2.2%. The average value of Nal-Eud tablets at this point in time is 33.3% and the deviation is 21.5%

Example 10 – Release behavior of the naloxone tablets from Example 8

Release of the active ingredients from various tablets was investigated by means of HPLC over a period of 12 hours using the basket method according to USP at pH 1.2.

A comparison of the values given in the tables with Figure 9 shows clearly that the release of naloxone does not change reproducibly regardless of how they are produced, even if the tablets are produced by extrusion.

Time (min)	Nal-Extr-A	Nal-Extr-B	Nal-Extr-C
	Nal	Nal	Nal
0	0	0	0
15	15.0	15.0	14.3
120	40.7	41.9	40.1
420	72.0	75.2	73.76
720	90.1	92.4	91.2

The release values are based on naloxone (line 2) and are given in percentage amounts. "Nal" stands for naloxone and indicates the active ingredient investigated. The average naloxone release in the case of Nal-Extr tablets amounts to 40.9% at 120 minutes. The maximum deviation at this measurement point in time is 2.4%.

Example 11 – Electron microscopic comparison of the structure of naloxone tablets from Example 7 and Example 8

For the electron microscopic examination, Nal-Eud tablets according to Example 7 with 5 mg naloxone (Nal-5-Eud) and a Nal-Extr tablet according to Example 8 were used.

Figures 10A and 10B show different magnifications of scanning electron micrographs of a Nal-5-Eud tablet. Figures 11A and 11B shows scanning electron micrographs of a Nal-Extr tablet with the inventive formulation.

It can be seen clearly from a comparison of the figures that the inventive formulation has a much finer and more homogeneously structured surface. Naloxone efflorescences can definitely be discerned in Figures 10A and 10B but not in Figures 11A and 11B. This structured difference may be the reason for the difference in the release behavior of the various preparations.

Example 12 – Electron micrographic structural comparison of naloxone granules from Example 7 and Example 8

Granules like those used to produce the Nal-Sure tablets according to Example 7 with 10 mg naloxone (Nal-10-Sure) and Nal-Extr tablets according to Example 8 were used for the electron microscopic examination.

Figures 12A and 12B show different magnifications of scanning electron micrographs of Nal-10-Sure granules. Figures 13A and 13B shows scanning electron micrographs of Nal-Extr granules with the inventive formulation.

It can be seen clearly here that independently of the production process, granules with an inventive formulation have homogeneously structured surfaces without any large cracks or efflorescences. Without being bound to a theory, it is assumed that these surface properties are responsible for the release behavior of inventive formulations.

Example 13 – Stability of naloxone tablets in storage as a function of the matrix used

Several tablets were produced with 5 mg naloxone as described in Example 7 using Eudragit® RS30D or Surelease® E-7-7050. The tablets were stored at 25°C and 60% relative humidity. At various points in time the release behavior was tested as described in Example 6.

Figures 14A and 14B and the tables show clearly that in the case of naloxone tablet formulated with Eudragit® RS30D, the release profiles differ after only a short storage time. For tablets formulated with Surelease® E-7-7050, however, the release is largely the same even after a storage time of 15 months.

Storage time (months)	0	1	3.5
Preparation (name)	Nal-5-Eud-0	Nal-5-Eud-1	Nal-5-Eud-3.5
Time (min)			
15	16.46	12.66	15.06
90	30.29	28.78	30.6
240	52.94	43.85	47.5
480	71.07	57.37	62.86
720	83.29	66.68	73.58
1020	91.61	73.03	80.97

Storage time (months)	0	3	6	15
Preparation (name)	Nal-5-Sure-0	Nal-5-Sure-3	Nal-5-Sure-6	Nal-5-Sure-15
Time (min				
15	21.58	22.52	16.04	24.36
120	49.94	49.05	51.93	55.59
420	79.83	86.32	87.99	88.49
720	91.74	97.55	100.27	97.07

The release is given in percentage amounts in the tables. The release of naloxone was tested in each case.

CLAIMS

1. Storage stable pharmaceutical formulation comprising one or more pharmaceutically active compounds in a diffusion matrix, characterized in that the essential release properties of the matrix are determined by ethyl cellulose or a polymer based on ethyl cellulose and at least one fatty alcohol and that the active compounds are released from the essentially non-swellable diffusion matrix in a sustained, invariant and, if several active compounds are present, independent manner.

2. The pharmaceutical formulation according to Claim 1, characterized in that the fatty alcohol is lauryl alcohol, myristyl alcohol, stearyl alcohol, cetylstearyl alcohol, ceryl alcohol and/or cetyl alcohol, especially preferably stearyl alcohol.

3. The pharmaceutical formulation according to Claim 1 or 2, characterized in that the formulation contains ethyl cellulose.

4. The pharmaceutical formulation according to any one of the preceding claims, characterized in that the formulation does not contain any relevant amounts of alkaline and/or water-swellable substances, in particular acrylic acid derivatives and/or hydroxyalkyl celluloses.

5. The pharmaceutical formulation according to any one of the preceding claims, characterized in that the formulation contains the usual pharmaceutical formulation excipients such as fillers, lubricants, antistick agents and/or plasticizers.

6. The pharmaceutical formulation according to Claim 5, characterized in that the fillers include sugar, preferably lactose, glucose and/or sucrose, starches and their hydrolysates, preferably microcrystalline cellulose and/or cellactose, sugar alcohols, preferably sorbitol and/or mannitol, sparingly soluble calcium salts, preferably calcium hydrogen phosphate, dicalcium phosphate or tricalcium phosphate and/or povidone.

7. The pharmaceutical formulation according to Claim 5, characterized in that the lubricants are magnesium stearate, calcium stearate and/or calcium laureate and/or fatty acids, especially preferably stearic acid.

8. The pharmaceutical formulation according to Claim 5, characterized in that antistick agents are highly dispersed silica, especially preferably Aerosil®, talc, cornstarch, magnesium oxide, magnesium stearate and/or calcium stearate.

9. The pharmaceutical formulation according to Claim 5, characterized in that the plasticizers comprise dibutyl sebacate.

10. The pharmaceutical formulation according any one of the preceding claims, characterized in that the formulation is stable in storage for at least 2 years under standard conditions (60% relative humidity, 25°C) so that it conforms to approval specifications.

11. The pharmaceutical formulation according any one of the preceding claims, characterized in that the active ingredients are opioid analgesics, preferably morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives thereof, methadone, dextropropoxyphene, buprenorphine, pentazocine, tilidine, tramadol and hydrocodone and/or opioid antagonists, preferably naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxonazine, methyl naltrexone, ketylcyclazocine, norbinaltorphimine, naltrindole, 6-β-naloxol and/or 6-β-naltrexol.

12. The pharmaceutical formulation according to Claim 11, characterized in that the opioid analgesic and/or antagonist is used in the form of its pharmaceutically acceptable derivatives having the same effect such as *the free base* or as the salts and the like, especially preferably as hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

13. The pharmaceutical formulation according Claim 11 or 12, characterized in that the formulation at least two active ingredients, namely oxycodone and naloxone, where oxycodone is present in a quantity range from 10 to 150 mg, preferably

10 to 80 mg and naloxone is present in a quantity range from 1 to 50 mg per unit dose.

14. The pharmaceutical formulation according Claim 13, characterized in that it contains oxycodone and naloxone in a weight ratio range from max. 25:1, preferably max. 20:1, 15:1, especially preferably 5:1, 4:1, 3:1, 2:1 or 1:1.

15. The pharmaceutical formulation according to Claim 11 or 12, characterized in that the formulation contains oxycodone or naloxone, where oxycodone is present in a quantity range from 10 to 150 mg, preferably 10 to 80 mg and naloxone is present in a quantity range from 1 to 50 mg.

16. The pharmaceutical formulation according to any one of the preceding claims, characterized in that the formulation is in the form of a tablet, preferably multilayer tablet, capsule, pill, granules and/or powder.

17. The pharmaceutical formulation according to Claim 16, characterized in that the dosage is suitable for oral, nasal and/or rectal administration.

18. The pharmaceutical formulation according to any one of the preceding claims, characterized in that the formulation is produced by buildup granulation or breakdown granulation, preferably by spray granulation.

19. The pharmaceutical formulation according any one of Claims 1 through 17, characterized in that the formulation is produced by extrusion.

20. Storage stable pharmaceutical formulation comprising one or more pharmaceutically active compounds in a matrix for delayed release of the active compounds, characterized in that the matrix is an essentially non-swellable diffusion matrix whose release properties are determined by amounts of ethyl cellulose or of a polymer based on ethyl cellulose and at least one fatty alcohol as matrix constituents and by extrusion or granulation of the matrix material with the amount of active compounds to form the matrix containing the active ingredient.

21. The pharmaceutical formulation that is stable in storage according to Claim 20, whereby the diffusion matrix is an essential non-erosive matrix.

22. The pharmaceutical formulation that is stable in storage according to Claim 20 or 21, whereby the matrix material contains ethyl cellulose.

23. The pharmaceutical formulation that is stable in storage according to any one of Claims 20 through 22, whereby the matrix is formed by extrusion, in particular by melt extrusion.

24. Storage stable pharmaceutical formulation comprising an effective amount of an opioid agonist and/or an opioid antagonist in an essentially non-swellable and non-erosive diffusion matrix, the release properties being determined by the amount of ethyl cellulose content or a polymer based on ethyl cellulose and at least one fatty alcohol.

25. The pharmaceutical formulation that is stable in storage according to Claim 24 having an active oxycodone content and/or naloxone content, whereby oxycodone is present in a quantity range from 10 to 150 mg, preferably 10 to 80 mg and naloxone is present in a quantity range from 1 to 50 mg per unit dose.

26. The pharmaceutical formulation that is stable in storage according to Claim 24 or 25 with an active oxycodone content and/or naloxone content whereby it contains oxycodone and naloxone in a weight ratio range from max. 25:1, preferably max. 20:1, 15:1, especially preferably 5:1, 4:1, 3:1, 2:1 or 1:1.

27. The method for producing a formulation according to any one of Claims 1 through 26, characterized in that it is a granulation method, preferably a buildup granulation and/or breakdown granulation method, especially preferably spray granulation.

28. The method for producing a formulation according to any one of Claims 1 through 26, characterized in that it is an extrusion process using contra-rotating or co-rotating single-screw or multi-screw extruders with or without compounding element(s).

29. The method according to Claim 28, characterized in that it is an extrusion method using contra-rotating twin-screw extruders, preferably without compounding elements.

30. The method according to Claim 28 or 29, characterized in that the temperature of the heating elements of the extruder is 20°C to 120°C, preferably 50°C to 100°C, especially preferably 50°C to 90°C and especially preferably 50°C to 70°C.

31. The method according to any one of Claims 28 through 30, characterized in that the diameter of the nozzle opening of the extruder is between 1 and 10 mm, preferably 2 to 8 mm, especially preferably 3 to 5 mm.

32. The method according to any one of Claims 28 through 31, characterized in that the resulting temperature in the extruder does not impair the stability of the active ingredients.

ABSTRACT

The invention relates to a pharmaceutical formulation that is stable in storage and contains preferably two active ingredients in a non-swellable diffusion matrix whereby the active ingredients are released from the matrix in a sustained and invariant manner and, when there are several active ingredients, in an independent manner, and the essential release properties of the matrix are determined by ethyl cellulose and at least one fatty alcohol. Furthermore, the invention relates to methods for producing such a pharmaceutical formulation.

Fig 1

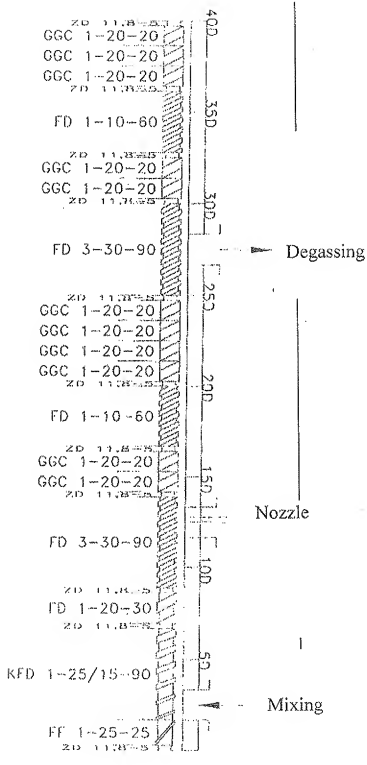
GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
FD 1-10-60
GGC 1-20-20
GGC 1-20-20
FD 3-30-90
GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
GGC 1-20-20
FD 1-10-60
GGC 1-20-20
GGC 1-20-20
FD 3-30-90
FD 1-20-30
KFD 1-25/15-90
FF 1-25-25
400
350
300
250
200
150
100
50
Degassing
Nozzle
Mixing

Fig 2

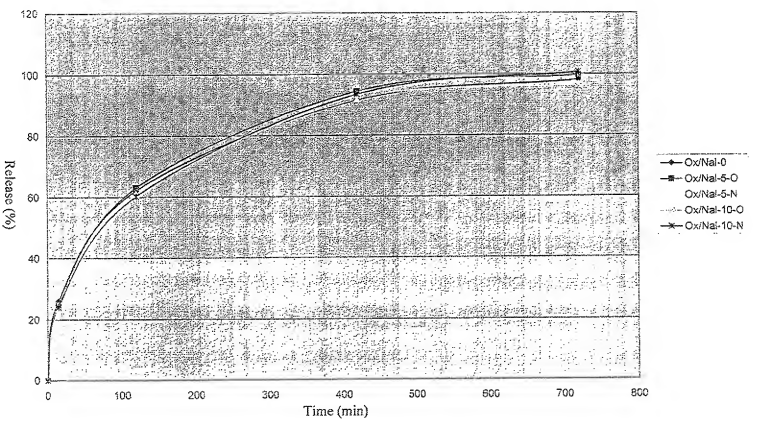
120
100
80
60
40
20
0
Release (%)
0
100
200
300
400
500
600
700
800
Time (min)
Ox/Nal-0
Ox/Nal-5-O
Ox/Nal-5-N
Ox/Nal-10-O
Ox/Nal-10-N

Fig 3A

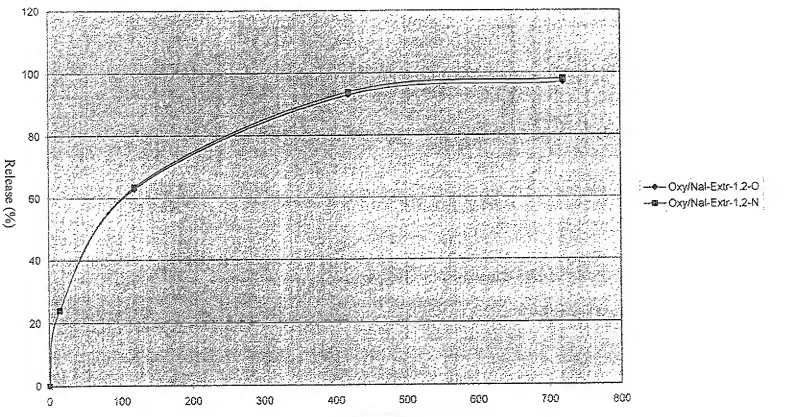
120
100
80
60
40
20
0
Release (%)
0
100
200
300
400
500
600
700
800
Time (min)
Oxy/Nal-Extr-1.2-O
Oxy/Nal-Extr-1.2-N

Fig 3B

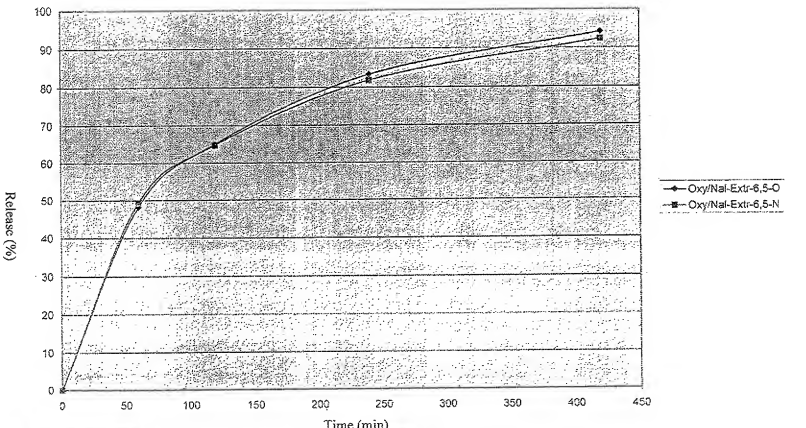
100
90
80
70
60
50
40
30
20
10
0
Release (%)
0
50
100
150
200
250
300
350
400
450
Time (min)
Oxy/Nal-Extr-6,5-O
Oxy/Nal-Extr-6,5-N

Fig 4A

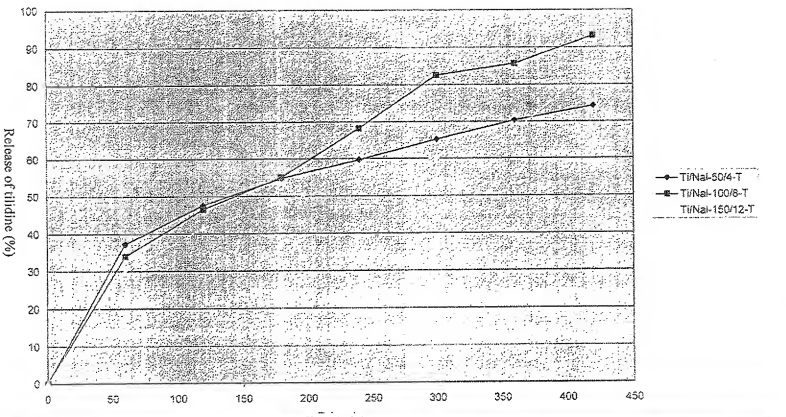
Release of tilidine (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
Time (min)
Til/Nal-50/4-T
Til/Nal-100/8-T
Til/Nal-150/12-T

Fig 4B

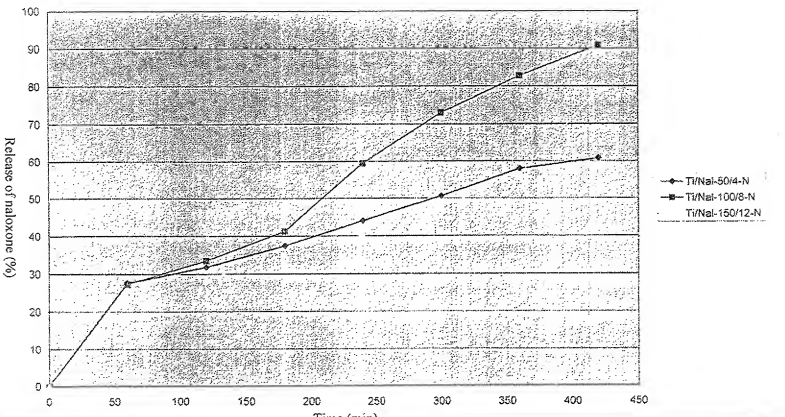
Release of naloxone (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
Time (min)
Ti/NaI-50/4-N
Ti/NaI-100/8-N
Ti/NaI-150/12-N

Fig 5A: Surface of the Ox/Nal-10 tablet, magnification 25X. Voltage 10 kV. Bar length 2 mm

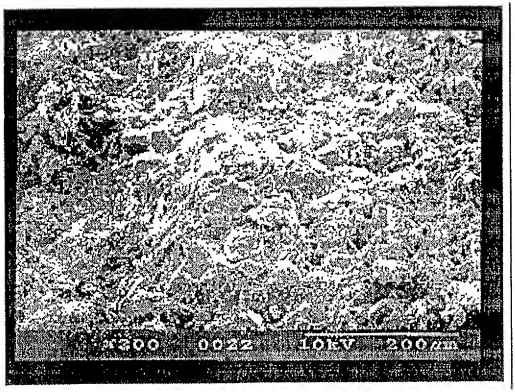

Fig 5B: Surface of the Ox/Nal-10 tablet, magnification 200X. Voltage 10 kV. Bar length 200 µm

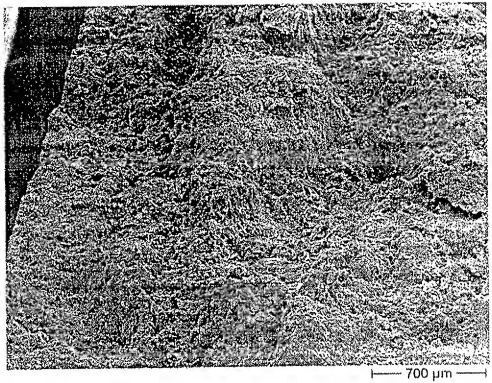

Fig 6A: Surface of the Ox/Nal extruded tablet, magnification 40X. Voltage 10 kV. Bar length 700 µm

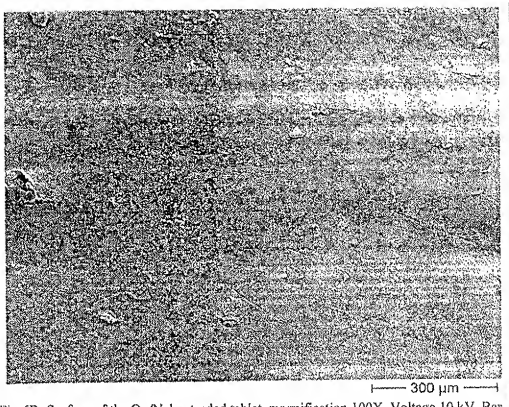

Fig 6B: Surface of the Ox/NaI extruded tablet, magnification 100X. Voltage 10 kV. Bar length 300 µm

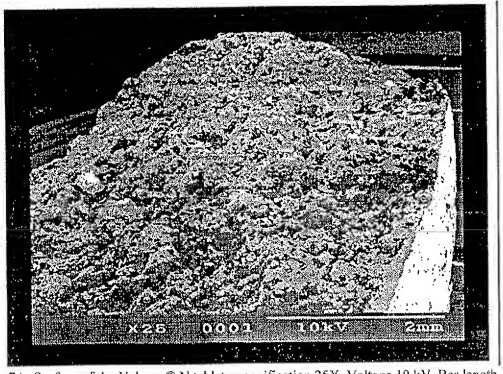

Fig 7A: Surface of the Valoron® N tablet, magnification 25X. Voltage 10 kV. Bar length 2 mm

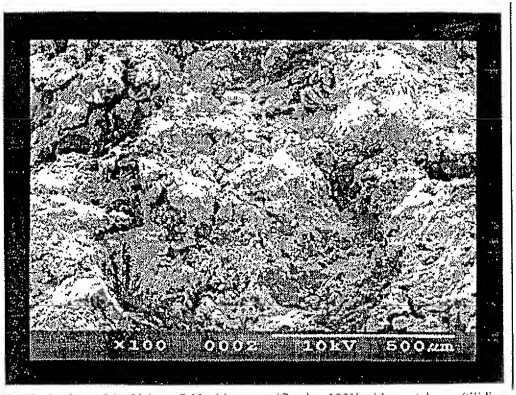

Fig 7B: Surface of the Valoron® N tablet, magnification 100X with crystal rose (tilidine, lower left). Voltage 10 kV. Bar length 500 µm